Coregulation of the APO-1 Antigen With Intercellular Adhesion Molecule-1 (CD54) in Tonsillar B Cells and Coordinate Expression in Follicular Center B Cells and in Follicle Center and Mediastinal B-Cell Lymphomas

By Peter Möller, Christof Henne, Frank Leithäuser, Annette Eichelmann, Annette Schmidt, Silke Brüderlein, Jens Dhein, and Peter H. Krammer

APO-1 is a 48-Kd transmembrane glycoprotein identical to the Fas antigen and belongs to the nerve growth factor (NGF)/tumor necrosis factor (TNF) receptor family of surface molecules. Cross-linking of APO-1 induces apoptotic cell death in sensitive cells. We show here that APO-1 is an activation molecule on B cells. It was induced/enhanced on dense and buoyant tonsillar B cells, respectively, through surface Ig cross-linking in combination with interleukin-2 or by interferon-γ together with tumor necrosis factor-α. These conditions also increased the amount of intercellular adhesion molecule-1 (CD54) on these cells. Epstein-Barr virus transformants of peripheral B cells coexpressed APO-1 and CD54 at very high levels. Immunohistologically, APO-1 was detectable at low levels in a subpopulation of follicle center B blasts and, at higher levels, in sinusoidal B cells. APO-1 was undetectable in follicular mantle B cells and plasma cells. In isolated tonsillar B cells, APO-1 was expressed in CD10+ follicle center cells. In acute B lymphoblastic leukemia, chronic B lymphocytic leukemia, and Burkitt’s lymphomas, APO-1 and CD54 molecules were immunohistochemically undetectable. Coordinate expression of these antigens was found in mediastinal B-cell lymphomas. The mode of APO-1 and CD54 expression was correlated in follicle center cell lymphomas (P < .0019), but less stringently in hairy cell leukemia. No association was found in plasmacytomas. This was in line with the differential expression of these molecules found in reactive plasma cells. Expression of APO-1 in B cells of different stages of differentiation and, correspondingly, in certain B-cell neoplasias might suggest a role of this molecule in the induction of B-cell apoptosis. This function might be influenced by CD54 and CD54-mediated signals.

MATERIALS AND METHODS

Tumor issues and lymphoma typing. To determine the physiologic expression of APO-1 and ICAM-1 (CD54) in B-cell subpopulations of the normal lymphoid system, cervical lymph nodes (including several specimens affected by toxoplasmosis lymphadenitis) and infantile thymus obtained during cardiacotomy were chosen as

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Submitted July 31, 1992; accepted November 24, 1992.

Supported by the Tumorzentrum Heidelberg/Mannheim, the Deutsche Krebshilfe (989-91), and the Deutsche Forschungsgemeinschaft (KR 776/3-1).

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0006-4971/93/8/100-00093 $00/0

Blood, Vol 81, No 8 (April 15), 1993: pp 2067-2075
Table 1. Expression of APO-1 and ICAM-1 (CD54) in Microtopographically and Cytomorphologically Distinguishable B-Cell Types as Determined by Immunohistochemistry

<table>
<thead>
<tr>
<th>Tissue</th>
<th>B-Cell Type</th>
<th>APO-1</th>
<th>ICAM-1 (CD54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic tonsil (n = 3)</td>
<td>Follicle center B cells</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td></td>
<td>Mantle zone B cells</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Intraepithelial B cells</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Plasma cells</td>
<td>-</td>
<td>-/+</td>
</tr>
<tr>
<td>Toxoplasmic lymphadenitis (n = 2)</td>
<td>Follicle center B cells</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td></td>
<td>Mantle zone B cells</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sinusoidal B cells</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Plasma cells</td>
<td>-</td>
<td>-/+</td>
</tr>
<tr>
<td>Normal infantile thymus (n = 4)</td>
<td>Medullary B cells</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>

Abbreviations: +, low; ++++, high antigen density as compared with positive reference cells; -, no detectable antigen.

reference organs. Previously immunophenotyped B-cell neoplasias were drawn from our bank of fresh-frozen tumor tissue. The series examined contained 4 lymph nodes involved by CD10⁺, CD19⁺ (data not shown) acute B-lymphoblastic leukemia, 12 lymph nodes involved by B-chronic B-lymphocytic leukemia, 8 spleens and 1 lymph node involved by hairy cell leukemia, 43 lymph nodes affected by different types of follicle center cell lymphomas (sub)classified using the updated Kiell classification of non-Hodgkin’s lymphomas²² and, alternatively, the Lukes/Collins classification²³, 8 Burkitt’s lymphomas of different primary sites, 25 specimens of primary mediastinal (thymic) B-cell lymphoma,²⁴²⁷ and 9 plasmacytomas.

Tissue processing. From the quick-frozen tissues, serial frozen sections of about 1 cm² in area and 4 to 6 μm in thickness were air-dried overnight, fixed in acetone for 10 minutes at room temperature, and immunostained immediately or stored at −20°C for 1 to 3 weeks.

Cell culture. Tonsillar B lymphocytes, peripheral blood B cells from two patients with chronic B-lymphocytic leukemia (B-CLL) and hairy cell leukemia, respectively, and 7 different EBV-transformed B-cell lines derived from peripheral and tonsillar B cells were used in this study. All cells were maintained in RPMI 1640 medium (GIBCO, Grand Island, NY) supplemented with 10% heat-inactivated fetal calf serum (FCS; GIBCO), 1 mmol/L glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin, and 2.5 μg/mL amphotericin B and cultured at 37°C in a humidified 5% CO₂ atmosphere.

Cell preparation. Tonsils were obtained from routine tonsillectomy. Tonsillar cell suspensions were obtained by mincing the tissue and pressing it through a stainless steel sieve. Mononuclear cells were isolated by Ficoll-Hypaque (Pharmacia, Piscataway, NJ) gradient...
centrifugation, followed by depletion of monocytes/macrophages by treatment with 2.5 mmol/L L-leucine methyl ester for 40 minutes at room temperature. Tonsillar B lymphocytes were prepared by two subsequent cycles of rosetting with 2-aminoethylisothouroum bromide (AET)-treated sheep red blood cells and Ficoll-Hypaque gradient separation. This procedure led to residual (CD3+) T-cell contaminations that were regularly below 3%. The enriched B lymphocytes were resuspended in 80% Percoll (Biochrom, Berlin, Germany) at approximately 5 × 10^6 cells/mL and layered under Percoll step gradients in 15-mL conical tubes with 3 mL of 70% (1.086 g/mL), 55% (1.069 g/mL), 40% (1.052 g/mL), and 30% (1.040 g/mL) Percoll. After centrifugation at 1,600g for 20 minutes, cells from the 40%/55% and 55%/70% Percoll interfaces were isolated and referred to as “D40/55” (buoyant B cells) and “D55/70” (dense B cells). “Buoyant” and “dense” B cells were stimulated with 0.001% formalinized bromide (AET)-treated sheep red blood cells and Ficoll-Hypaque with Hams’ hematoxylin. Approximately 10⁶ cells per sample, suspended in 50 μL of medium, were incubated at 4°C with an equal volume of the appropriate dilution of each MoAb. After 45 minutes, cells were washed twice in 500 μL of cold medium, and 2 μM of F(ab’)₂ goat antigoat IgG and IgM fluorochrome isiothiocyanate (FITC) conjugate (Jackson Immunoresearch, West Grove, PA) was added for 45 minutes at 4°C. Cells were washed again twice and resuspended in 300 μL of medium containing 1 μg/mL propidium iodide (Sigma, St Louis, MO). From each sample the green fluorescence of 10⁶ cells was analyzed. For double-labeling experiments, bound biotinylated second antigen via unconjugated primary antibody detected by affinity-purified Fc-specific dichlorotriacinylaminofluorescein-conjugated (Fab’), fragment goat-antimouse IgG (Jackson). Dead cells were removed from analysis by selectively gating on propidium iodide fluorescence, using forward and side scatter parameters. Flow cytometry was performed on a FACScan cytometer with the LYSYS II software (Becton Dickinson).

Immunohistologic staining procedures. The method is described in detail elsewhere.28 MoAbs in culture supernatants were used undiluted, ascertained preparations were used as 1:200 dilutions, and purified reagents were used in a protein concentration of 10 μg/mL. A polyclonal biotinylated sheep antibody to mouse Ig (reactive with all mouse isotypes) and a streptavidin-biotinylated peroxidase complex, all obtained from Amersham (High Wycombe, UK), served as a detection system for the primary antibodies. 3-Amino-9-ethylcarbazole (Sigma) was used as substrate for the enzyme; the peroxidase reaction resulted in an intense red precipitate. The sections were faintly counterstained with Harris’ hematoxylin.

Controls and evaluation of antigen density in tissue sections. Negative controls were performed without the primary antibody in each individual case and, in a limited number of cases, by using several irrelevant MoAbs of different mouse Ig isotypes and directed against nonhuman antigens. No staining was observed, except for the reaction of granulocytes whose endogenous peroxidase was not destroyed. Strongly stained dendritic stromal cells, histiocytic cells, and/or T-lymphocytes, always present in various amounts, served as intrinsic positive controls. At the same time, they were taken as internal parameters for the maximum reactivity, which was regarded as “high antigenic density” and symbolized by “+++.” A definitely weaker staining intensity of the target cell population was characterized as “low antigenic density” and symbolized by “+.” The absence of specific staining was symbolized by “−.” Whenever the staining intensity within a B-cell compartment was heterogenous, a simple semiquantitative statement was made. For comparative visualization of the entire B-cell population, a CD19 immunostaining in combination with a CD38 staining was used.

Statistical analysis of immunohistochemical results. Fisher’s exact test was applied for analysis of contingency tables.

RESULTS

APO-1 and CD54 expression in normal B cells. As shown by immunohistochemistry, APO-1 expression at low levels was regularly detectable in a major subpopulation of follicle center B blasts (Table 1 and Fig 1a and b). These cells were located in the basal, so-called dark zone of the follicle centers (FC) and could clearly be distinguished from follicle dendritic cells, which in this site were devoid of APO-1. In the light zone of the follicle center, the assessment of APO-1 expression in B blasts was hampered by the strongly stained dendritic network. Mantle zone B lymphocytes (MZ) and mature plasma cells were unstained in all sites examined. Epithelium-associated (EF) B cells that morphologically resemble small, cleaved follicle center B cells in the mucosa-associated lymphoid tissues (Fig 1a) and that have small dendritic cytoplasmic extensions within the thymic medulla lacked detectable APO-1 (Fig 2a and b). Sinusoidal (synonymous monocytoid) B cells giving rise to the so-called sinusoidal B-cell reaction (as seen in toxoplasmic lymphadenitis and lymphadenopathy due to early human immunodeficiency virus [HIV] infection) expressed APO-1 at high levels (Fig 2c). APO-1 expression in follicle B cells essentially corresponded to that of ICAM-1 (CD54). Although serial section analysis showed the existence of APO-1⁺ and CD54⁺ center B blasts, the majority of these cells carried both antigens at the cell surface (Fig 1b and c). However, outside the follicle, considerable differences emerged: sinusoidal B cells were APO-1⁺-positive (Fig 2c) at high levels, but lacked CD54 (Fig 2d). Vice versa, CD54 was expressed at high levels in thymic medullary B cells in the absence of detectable APO-1. Furthermore, plasma cells in/on which APO-1 was undetectable expressed CD54 in the (extrafollicular) subpopulation. These results could be supported in part and extended by cytometric analysis of tonsillar B-cell isolates (Table 2).

Small “dense” B cells (physical density 55%/70%) were practically devoid of APO-1 and expressed CD54 at low levels. By contrast, large, “buoyant” B cells (physical density 40/
Fig 2. Serial frozen section of normal infantile thymus stained for CD19 (a) and APO-1 (b); arrows mark the same Hassall's corpuscle in both sections (original magnification × 124). The medullary B-cell population expresses CD19 in high antigen density. The staining for APO-1 shows expression of the molecule on thymic epithelium, whereas the entire lymphoid population, ie, thymocytes and medullary B cells, is unstained. (c and d) Serial section of a lymph node showing the sinusoidal (monocytoid) B cells in a case of toxoplasmic lymphadenitis (original magnification × 257). The sinusoidal B cells express APO-1 at a high level (c); however, they are ICAM-1 (CD54)−negative (d). MZ marks the adjacent follicular mantle zone with APO-1−/CD54− cells.

55%) coexpressed both molecules at higher levels (Table 2; Fig 3a). In a double-labeling flow cytometric experiment (Fig 3b), it could be further substantiated that the buoyant fraction contained APO-1+ follicle center B cells. The dense fraction (physical density 55/70%) was mainly composed of APO-1−IgD+ cells (71.7%), whereas the majority of the buoyant fraction (physical density 35/50%) consisted of APO-1+IgD− cells (63.5%). Immunohistochemically, surface expression of IgD in tonsillar B cells is restricted to the mantle zone. In peripheral B cells, CD10 expression is restricted to the follicle center stage of maturation.29 As shown in Fig 3b, the majority of APO-1+ B cells in the buoyant fraction (53.1%) coexpress CD10. Only 1.9% of buoyant B cells were CD10− but lacked APO-1. Thus, it can be concluded that nearly all follicular center B cells expressed APO-1. In contrast, only a small percentage of dense B cells expressed CD10 and/or APO-1. Particularly in the buoyant fraction, double-labeling further showed an APO-1−/IgD+ subpopulation (19.1%), whereas in the dense fraction this double-positive population was negligible (3.0%). In this experiment, 14.5% of dense cells and 7.7% of buoyant cells were APO-1−/IgD+. These APO-1−/IgD+ cells may be derived from the intraepithelial (EF) compartment of the tonsil.

In vitro, expression of APO-1 and CD54 was coordinately enhanced by activation signals. Short-term cultures showed that stimulation through a combination of IFN-γ and TNF-α led to a minor increase of surface APO-1 and CD54 that was more distinct in the dense B-cell fraction (Fig 4a). Furthermore, SAC/IL-2 had an inducing/enhancing effect on tonsillar B cells that was more pronounced in the buoyant fraction (Fig 4b).

APO-1 and CD54 expression in EBV-transformed B lymphocytes. LCL resulting from EBV transformation of both peripheral and tonsillar B cells showed levels of APO-1 and CD54 expression that regularly exceeded that of in vitro-activated tonsillar B cells by about five times (Fig 5).

APO-1 and CD54 expression in B-cell neoplasias. The compiled immunohistochemical data on APO-1 and CD54 expression in B-cell leukemias and lymphomas are shown in
APO-1 expression on purified tonsillar B lymphocytes as determined by flow cytometry. (a) B lymphocytes isolated from the 40/55% and 55/70% Percoll interface referred to as “buoyant” (- - -) or “dense” (----). (b) Threshold for positivity. (c) Two-color flow cytometric analysis of slgD, CD10, and APO-1 expression on freshly isolated buoyant and dense tonsillar B cells (Percoll densities D35/50 and D55/70). Dichlorotriacinylaminofluorescein and streptavidin-phycoerythrin fluorescence is plotted on the x and y axis, respectively. Each dot plot analysis is based on 20,000 events.

Our results show that APO-1 is expressed at relatively low levels in the majority of follicle center B blasts and that
expression is abrogated at the plasma cell stage. Between these stages, APO-1 is transiently upregulated in B cells that undergo the so-called sinusoidal B-cell reaction. This is a state of activation associated with a monocytoid cytology taking place in the intrasinusoidal and perisinusoidal region of the lymph node (for review see Möller and Mielke29). On functional grounds, the monocytoid B cell is still poorly understood: it may represent the activated memory cell,29,30 APO-1 staining intensity of sinusoidal B cells is, although slightly less intense, comparable to that of LCL tumors transplanted into severe combined immunodeficiency (SCID) mice.27 In vitro, activation of tonsillar B cells via SAC/IL-2 or via IFN-γ in combination with TNF-α did not lead to the very high level of surface APO-1 expression regularly detectable in LCLs. This suggests an abnonormal hyperexpression of APO-1 in LCL that may be a consequence of EBV transformation. B-cell leukemias and Burkitt’s lymphoma show APO-1 expression at very low levels (ie, below the sensitivity or at the threshold of indirect, enzyme-mediated immunohistochemistry) or are APO-1−, respectively. Follicle center cell lymphomas were heterogenous, although abnormally high levels of APO-1 prevailed. High APO-1 antigen density was characteristic for mediastinal B-cell lymphoma. This type of medium to large cell lymphoma originating in the thymus has been shown to bear immunophenotypic similarities with sinusoidal B cells27 and features considerable apoptotic rates in situ.24

In vitro1,2 and in vivo3,4 data suggest that APO-1 is a receptor for a physiologic apoptotic signal. If this were the case, one would expect APO-1 expression on B cells in developmental stages characterized by the occurrence of apoptosis. In B-cell ontogeny, apoptosis is prominent in the follicle center. A high apoptotic rate of B cells was shown to be correlated with the absence of bcl-2 expression.31,32 Accordingly, follicle center B blasts are devoid of bcl-2 protein.33 Interestingly, APO-1 is expressed in at least a subset of follicle center B blasts. This might be in line with a role of APO-1 in intrafollicular B-cell apoptosis. The highest expression of APO-1 in normal B cells, however, was found in sinusoidal B cells.

Table 3. Expression of APO-1 and ICAM-1 (CD54) in B-Cell Leukemias and Lymphomas as Determined by Immunohistochemistry

<table>
<thead>
<tr>
<th></th>
<th>APO-1</th>
<th>ICAM-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Stringent correspondence:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute B-lymphoblastic leukemia</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Chronic B-lymphocytic leukemia</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Mediastinal (thymic) B-cell lymphoma</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Statistical correlation (P &lt; .0019):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular center cell lymphoma</td>
<td>43</td>
<td>10</td>
</tr>
<tr>
<td>Unqualified relation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Differential expression:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

Abbreviations: +, low; ++++, high antigen density as compared with positive reference cells; −, no detectable antigen.
APO-1 expression in B-cell lymphoma. (a) A primary mediastinal B-cell lymphoma, large-cell variant. As an exception for this type of tumor, the neoplastic population is devoid of APO-1, whereas the reactive infiltrate (mainly composed of T cells, data not shown) expresses this molecule at high levels (original magnification × 129). (b) A follicular lymphoma predominantly composed of centrocytic (small cleaved) cells featuring a sclerosing reaction expresses APO-1 at a low level (original magnification × 64).

In areas of sinusoidal B-cell reaction, apoptotic figures are rare (Möller, unpublished), suggesting that apoptosis does not occur in this microenvironment. It can thus be speculated that, under physiologic conditions, surface expression of APO-1 in B lymphocytes might not be associated exclusively with imminent cell death. The APO-1 molecule might also transduce alternative signals, possibly depending on the presence or the absence of different molecules functionally linked with APO-1.

We show that in the buoyant fraction of tonsillar B-cell isolates, APO-1 is coexpressed with ICAM-1 (CD54). Furthermore, both molecules are coordinately upregulated by IFN-γ and TNF-α and also by SAC in combination with IL-2. These data confirm findings of Webb et al., Tohma et al., and Padros et al. as to CD54 expression in normal B cells. However, the fact that a subset of follicle center B blasts is CD54⁺ is at variance with Dustin et al. Immunohistochemically, we found a coordinate expression of APO-1 and CD54 in a subset of follicle center B blasts and a noncoordinated expression of both molecules in thymic medullary B cells (APO-1⁻, CD54⁺), in a subset of plasma cells (APO-1⁻, CD54⁺), and in sinusoidal (syn. monocytoid) B cells (APO-1⁺, CD54⁻).

Confirming published data, our examination of CD54 expression in LCL and B-cell neoplasias yielded high antigen levels in LCL, an absence of CD54 in Burkitt’s lymphoma and in B leukemias, heterogeneous CD54 expression in follicle center cell lymphomas, and CD54 positivity in most plasmacytomas. APO-1 and CD54 were coordinately expressed in LCL, in mediastinal B-cell lymphoma, in the majority of follicle center cell lymphomas, and, eventually, in hairy cell leukaemia. APO-1 expression in the absence of CD54 was generally rare but was found in a minority of follicle center cell lymphomas.

ICAM-1 (CD54) on B cells binds the ligand LFA-1 (CD11a/CD18) on T cells. This interaction was shown to confer stimulatory signals to the B cell during (cognate) interaction. The natural ligand for APO-1 is unknown. If this ligand were cell-bound, one might speculate that CD54 might serve a similar costimulatory function modulating the APO-1 mediated signal.

Table 4. Heterogenous Expression of APO-1 and CD54 in Follicular Center Cell Lymphomas

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>APO-1</th>
<th>CD54</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Centroblastic</td>
<td>Centrocytic</td>
</tr>
<tr>
<td></td>
<td>(no.)</td>
<td>(no.)</td>
</tr>
<tr>
<td>+++t</td>
<td>+++t</td>
<td>6</td>
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<tr>
<td>-</td>
<td>+++t</td>
<td>0</td>
</tr>
</tbody>
</table>

* Classification according to Stansfeld et al.
† See legend to Table 1.

**ACKNOWLEDGMENT**

We thank G. Moldenhauer, MD (German Cancer Research Center) and B. Dörken, MD (Medizinische Klinik und Poliklinik V, University of Heidelberg) for contributing the MoAb CD19 (HD237), K. Voelker, MD (Heilig-Geist-Hospital Bensheim) for providing tonsils, and K.M. Debatin, MD (Universitätskinderklinik, University of Heidelberg) for fruitful discussions. The excellent technical assistance of A. Müller, S. Westenfelder, and J. Moyers is gratefully acknowledged.

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Coregulation of the APO-1 antigen with intercellular adhesion molecule-1 (CD54) in tonsillar B cells and coordinate expression in follicular center B cells and in follicle center and mediastinal B-cell lymphomas

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